

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

DIGESTIVE DISEASES

Digestive diseases such as peptic ulcers, gallstones, and liver disorders are a major health problem in the United States today. Twenty million Americans are treated for some type of chronic digestive disease each year, and according to the National Digestive Diseases Advisory Board, almost half the U.S. population suffers a digestive problem at some time.

Over the last 35 years, however, the efforts of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) to increase the understanding of digestive diseases have contributed to better diagnosis, treatment, and prevention of these health problems.

For example, in 1960, over 3,000 Americans died from inflammatory bowel disease (IBD), primarily Crohn's disease and ulcerative colitis. By 1980, that figure had dropped to well below 800.

The development in the 1970's of new drugs such as cimetidine, ranitidine, and sucralfate has dramatically improved the outlook for people with peptic ulcers. In fact, according to the National Center for Health Statistics, the number of peptic ulcer patients requiring hospitalization for treatment of their condition dropped 43 percent between 1970 and 1980.

New Digestive Disease Centers

NIADDK has recently established 10 digestive disease research centers to enhance the effectiveness of groups of research scientists who study digestive diseases and disorders. There are now 13 federally supported centers across the United States devoted to the study of diseases of the digestive system. Each of these centers brings together both basic scientists such as immunologists and biochemists and clinicians such as surgeons, endoscopists, and radiologists. The centers make possible cooperative research among these investigators by making centralized resources available for research projects and by encouraging new investigations and collaborations in the area of digestive diseases.

Three of the centers are devoted to the study of liver and biliary tract diseases. The center at Yale University in New Haven, Connecticut, is under the direction of Dr. James Boyer and is devoted to the study of liver structure, function, and disease. This center studies: liver transport function and bile formation; bilirubin metabolism and the effects of alcohol; mechanisms of liver fibrogenesis (growth of fibrous

tissue in the liver commonly caused by cirrhosis and other disorders); blood flow to the liver and other digestive organs; and the evolution of chronic liver disease treatments, including liver transplantation.

Dr. Joseph Bloomer directs the liver center at the University of Minnesota at St. Paul. Research at this center is focused in three areas: abnormal liver metabolism due to both inherited and acquired liver disorders; liver damage due to viral hepatitis; and liver transplantation.

Dr. Francis Simon directs the hepatobiliary research center at the University of Colorado at Denver where researchers are studying: bile secretion disorders, which may be involved in drug toxicity, cholesterol gallstone disease, and jaundice; disorders of liver lipid metabolism, which may cause cholesterol gallstones and atherosclerosis; and liver cell injury caused by hepatitis B, drugs, metals, and liver cancer.

The center at the New England Medical Center in Boston is under the direction of Dr. Mark Donowitz, and is involved in studying 1) the processes by which materials are absorbed into and secreted out of the body through the gastrointestinal tract; and 2) the diseases that can arise from abnormalities in these processes, especially diarrhea, malabsorption syndromes, and jaundice.

Dr. Don Powell is director of the center at the University of North Carolina at Chapel Hill. Scientists there are focusing their research on diarrhea, irritable bowel syndrome, and IBD. A unique aspect of this center is its collaboration with North Carolina State University's School of Veterinary Medicine, where animal models for the study of these diseases may be developed.

Dr. William Snape directs the new center at the Harbor-UCLA Medical Center in Torrance, California, which is devoted to the study of IBD. Two areas of research emphasis are: examining the immunologic responses of IBD patients and mapping genetic abnormalities that may determine a person's predisposition for IBD.

Research at the center located at the Mayo Clinic and Foundation in Rochester, Minnesota, is under the direction of Dr. Sidney Phillips and is focused on the control of several functions of the digestive tract, including digestion, absorption, and motility. Investigators at this center are studying common diseases such as nonulcer dyspepsia, functional diarrhea, irritable bowel syndrome, and constipation, that result when these functions are disturbed.

Dr. Tadataka Yamada directs the research center at the University of Michigan at Ann Arbor. Scientists there are studying gastrointestinal peptide hormones, which are involved in appetite regulation, digestion, motility, secretion, and nutrient absorption. This work may help researchers better understand the role of gut hormones in the development of a wide range of illnesses such as obesity, peptic ulcer, irritable bowel syndrome, and diarrhea.

Dr. James Christensen oversees the activities of the center located at the University of Iowa in Iowa City. Their investigations are focused on the mechanisms of gastrointestinal motility, absorption and transport processes, and the neuro-anatomy of the digestive tract. One group of scientists is examining the effects of exercise on motility in the digestive tract. This work may help to explain why long distance runners and other participants in intense exercise often experience nausea, abdominal cramps, and sometimes bloody diarrhea.

Dr. William Silen, using the shared facilities of Harvard University, Beth Israel Hospital, and Brigham and Women's Hospital in Boston, leads a group of investigators studying the structure and function of the smooth muscle and the epithelium throughout the digestive tract. This research may lead to a better understanding of various digestive tract processes such as the defense mechanisms that protect the stomach and duodenum against injury from gastric acid secretions.

Gallstones

An estimated 25 million Americans suffer from gallstone disease, a problem that costs \$1 billion in surgical expenses annually. About 1 million new cases of gallstones are discovered each year.

New Method for Dissolving Gallstones Is Under Study

Dr. Johnson Thistle, an NIADDK grantee at the Mayo Foundation, has successfully dissolved gallstones in patients with a new nonsurgical procedure that uses a solvent called methyl tertiary butyl ether (MTBE). The technique, performed under local anesthesia, involves the placement of a catheter (a very thin, flexible tube) through the abdomen into the gallbladder. Small amounts of MTBE were then injected through the catheter directly into the gallbladder. A constant flushing of fresh solvent was continued throughout the procedure. Within hours the stones in each of the patients had begun to dissolve. If further research proves this technique to be a viable alternative to abdominal surgery for removing gallstones, it will provide not only enormous cost savings but also a safer procedure, especially for those patients at high risk.

Liver Diseases

The liver performs many complex biochemical tasks. As the largest internal organ in the human body, the liver functions as a "chemical factory." It purifies and detoxifies blood, stores certain nutrients, produces a variety of blood proteins, and secretes fluids such as bile that aid in digestion and waste removal. The liver is particularly vulnerable to many types of disease, and each year over 25,000 Americans die from chronic liver disorders.

New Drugs Available for Treating Familial Hypercholesterolemia

Using a combination of two drugs, NIADDK grantee Dr. Scott Grundy at the University of Texas Health Science Center in Dallas has significantly lowered blood cholesterol levels in patients with familial hypercholesterolemia. This disease is marked by extremely high levels of cholesterol in the bloodstream, which may lead to an early death from heart attack. The disorder is caused by a genetic defect that reduces the liver's ability to remove cholesterol from the bloodstream.

Dr. Grundy first gave his patients mevinolin, a drug that inhibits the liver's own production of cholesterol. As a result, the liver activated more of its cell receptors that are specially designed to take up cholesterol from the blood. The uptake of blood cholesterol by these receptors not only replenished the liver's supply of cholesterol but also reduced blood cholesterol levels by about 30 percent. Blood cholesterol levels were further reduced by administering a drug called compactin, which acts to remove bile acids--materials produced from liver cholesterol. The liver's need to replace the depleted supply of bile acids further increased its uptake of blood cholesterol, resulting in an overall 50 percent drop in blood cholesterol levels. This new treatment holds great promise for patients with familial hypercholesterolemia.

Evidence of Non-A, Non-B Hepatitis Virus Found

NIADDK intramural scientist Dr. William Coleman, Jr., and his colleagues at the Food and Drug Administration and the University of Goteborg in Sweden reported a significant breakthrough in hepatitis research with the identification of an enzyme that is involved in the proliferation of the virus believed to cause non-A, non-B hepatitis. Because screening tests for type B hepatitis have almost eliminated the transmission of this disease by blood transfusion, non-A, non-B hepatitis has become the most common form of hepatitis transmitted through blood transfusions.

About 580,000 cases of hepatitis occur in the United States each year, of which 120,000 are believed to be non-A, non-B hepatitis. The identification of markers of this virus

is important because it may lead to the development of a screening test to detect the non-A, non-B virus in blood bank supplies and may someday lead to a vaccine to prevent the disease.

Inflammatory Bowel Disease

Both Crohn's disease and ulcerative colitis are chronic inflammatory disorders of unknown cause that affect the intestinal tract and can result in diarrhea, abdominal pain, blood in the stool, and fever. An estimated 2 million Americans suffer from one or the other of these inflammatory bowel diseases. Although certain drugs can control the symptoms of Crohn's disease and ulcerative colitis, there is no known cure for either of them.

Scientists are studying naturally occurring materials that may affect inflammation in the bowel. Certain compounds related to prostaglandins (a group of naturally occurring fatty acids) are known to have an effect on inflammation in various parts of the body. Researchers at several NIADDK-supported institutions, including the newly funded IBD center at Harbor-UCLA Medical Center in Torrance, California, are examining the possible role of these compounds in the inflammation that occurs in IBD.

Mucus Defect Found in Ulcerative Colitis Patients

Drs. Kurt Isselbacher and Daniel Podolsky, NIADDK grantees at Massachusetts General Hospital in Boston, have found that when compared both to Crohn's disease patients and to healthy individuals (they weren't patients) used as controls, patients with ulcerative colitis have a genetically altered form of mucin, a component of the mucus normally found in the lining of the intestinal tract. The investigators will try to determine if this genetic-based difference plays a role in the onset of ulcerative colitis.

Acute Mesenteric Ischemia

Acute mesenteric ischemia (AMI) is a common condition that occurs when a blood vessel becomes blocked, cutting off the supply of blood to a section of the intestinal tract. This can lead to irreversible intestinal tissue damage and possible infection caused by the spread of bacteria into the wall of the diseased intestines. It is difficult to detect AMI between the time of blockage and subsequent tissue damage without subjecting patients to expensive, time-consuming, and occasionally dangerous examinations.

New Test Developed for Diagnosing AMI

Dr. Gregory Bulkley, an NIADDK grantee at the Johns Hopkins University in Baltimore, Maryland, has used animal models to develop a new technique for detecting AMI at its early stages when tissue damage is still reversible.

The technique involves injecting into the abdominal cavity, a solution containing small amounts of radioactive xenon gas, which emits gamma rays. Once in the abdomen, the xenon is absorbed into the intestines. If blood flow is normal, the xenon is rapidly cleared by the bloodstream and carried to the lungs where it is exhaled. However, in tissue where blood vessel blockage has occurred, the xenon remains trapped. After the xenon has been injected, images of the intestinal tract are made with a camera that picks up gamma rays. These images will show any trapped pockets of xenon that may have formed, thus pinpointing the location of possible blockages. The development of this test is important because it holds great promise as a safe and effective means for early detection of AMI in humans.

Diarrheal Diseases

Diarrhea is not only a major health problem but also a major cause of disability in the United States. At best, diarrhea can be distressing, but in more serious cases it can be debilitating and even life-threatening, especially in children, when it leads to dehydration and chemical imbalances in the blood of electrolytes such as sodium and potassium.

Somatostatin: Potential Treatment of Diarrheal Syndromes

Unfortunately, it is not always possible to determine the cause of diarrheal conditions. In such cases, therapy usually involves treating the diarrhea itself. The most effective drugs currently used for treating diarrhea are derivatives of opium such as paregoric. However, in some people these drugs may have serious side effects on the central nervous system.

Somatostatin is a naturally occurring substance in the body that exhibits several antidiarrheal effects. Previous research has shown that somatostatin given to rats stimulates sodium and chloride absorption and inhibits water and electrolyte secretions in the animals' intestinal tract. The substance also has been shown to decrease intestinal motility and to inhibit the release of hormones that may stimulate diarrhea.

Because somatostatin affects many organ systems throughout the body, NIADDK grantee Dr. Kiertisin Dharmasathaphorn at the University of California at San Diego has developed several variations of somatostatin that specifically act on the digestive tract. Results from this research may lead to an effective treatment for diarrhea.

National Cancer Institute

An estimated 59,900 Americans will die of cancers of the colon and rectum in 1985, making this the second leading cause of death from cancer.

Dr. Paul H. Sugarbaker, an intramural scientist of the National Cancer Institute (NCI), has been studying the survival outcome of patients who had surgery to remove colorectal metastases in the liver. This experience has shown that approximately 30 percent of patients who have had liver resections (removal of part of the liver) are alive and free of cancer 5 years later. This new surgical approach to the treatment of metastatic cancer has also been shown to be successful for the removal of sarcoma (cancers derived from supportive or connective tissues) metastases to the lungs.

Research efforts are being directed toward improving the results of this treatment by delivering chemotherapy directly to the tumor site. If cancer comes back after liver resection, 80 percent of the patients experience recurrences within the liver. The current approach, used at NIH, the University of Michigan, and the University of Alabama, is to inject chemotherapy directly into the major artery or vein that supplies the liver. Alternatively, a standard cancer drug 5-fluorouracil (5-FU) can be given into the intraperitoneal cavity by a dialysis catheter. This local-regional chemotherapy maximizes the dose of the drug to the organ at high risk for recurrent disease, the liver, and minimizes toxic side effects for the rest of the body.

NCI grantee Dr. Stanley E. Order and colleagues at the Johns Hopkins University, under a research grant from NCI, has developed the first effective treatment for primary liver cancer using radioactive antibodies to attack cancer cells. This therapy has tripled the average remission time and dramatically reduced the size of these cancers.

In 104 patients with liver cancer, almost half have gone into remission and approximately 7 percent are in total remission. The usual remission rate is 15 percent, and patients survive an average of 3 to 4 months after the standard treatments begin.

With the new therapy, one patient has lived free of cancer for almost 4 years. In another case, a 15-pound tumor was reduced to 2 pounds after a year's treatment, Dr. Order reported. Patients are given irradiation and two injections of antibodies containing radioactive iodine. The antibodies seek out antigens, or proteins, on the surface of the cancer cells and begin to destroy the liver cancer cells.

Surgery with combined radiation is the standard form of therapy for colon cancer. New chemotherapeutic approaches are being studied under NCI-supported funding at the Mayo Clinic by Dr. Charles G. Moertel. He is investigating whether vitamin C does in fact cure cancer, a popular theory advanced by Nobel Prize winner Linus Pauling.

Vitamin C was given to 50 patients with an advanced form of colon cancer who had not received prior chemotherapy. Another 50 patients were given sugar pills. Dr. Moertel found that vitamin C therapy was no more effective than the placebo therapy for improving either the interval between the beginning of treatment and disease progression or patient survival. On the basis of this and a previously funded study, high-dose vitamin C therapy was found ineffective against cancer.

Dr. Moertel and colleagues are also part of a NCI-funded cooperative treatment program called the North Central Cancer Treatment Group. They have been studying the efficacy of adjuvant chemotherapy after surgery for colon cancer that had spread to the liver.

Twenty six patients were given 5-fluorouracil following surgery to the colon and liver to see if the drug increased patient survival. The researchers found that patients receiving 5-fluorouracil did not live any longer than those patients who had surgery alone.

Photodynamic therapy with hematoporphyrins is a new treatment technique for a variety of gastrointestinal cancers being developed by Dr. Thomas J. Dougherty at the Roswell Park Memorial Institute in Buffalo, New York.

In the latest animal experiments, a certain wavelength of light was delivered to the tumor site. The treatment destroyed the tumor without injuring normal surrounding tissue. Additional work is now under way to test appropriate energy doses.

National Institute of Dental Research

Salivary glands are an integral part of the digestive system because they secrete certain enzymes, which initiate the breakdown of complex sugars, proteins, and other macromolecules. Salivary glands also secrete immunoglobulins, which protect against infection. Furthermore, by lubricating oral tissues and coating food into a bolus to be transferred to the pharynx, saliva plays a key role in the initiation of swallowing. NIDR research in digestive diseases includes investigations into the functional development and regulation of salivary glands, the composition of saliva, and salivary gland secretions under normal conditions and in certain disease states such as cystic fibrosis and the sicca syndrome (Sjogren's syndrome)--an autoimmune disorder whose symptoms include dry mouth and dry eyes.

Xerostomia, or dry mouth, is an area of particular concern to NIDR because a significant decrease in salivary flow or alteration in the composition of saliva can affect both oral and dental health and nutritional status. Dry mouth is a symptom of certain disorders such as the sicca syndrome and is also a common side effect of over-the-counter and prescription drugs and of radiation therapy. The most common manifestations of dry mouth are an increase in dental caries, gingivitis, and mucosal lesions. NIDR intramural researchers Drs. Phillip Fox and Bruce Baum are studying the functions of salivary glands during normal aging and in individuals with abnormal oral function due to disease or therapeutic procedures. Through studies in their Dry Mouth Evaluation Clinic, these investigators have developed a treatment protocol that has been successful in selected patients with dry mouth.

The drug pilocarpine induces saliva production in patients with salivary glands that are capable of functioning but that do not produce enough saliva. In addition, Drs. Fox and Baum are studying the effect of diminished saliva on swallowing, together with NIH Clinical Center colleague Dr. Barbara Sonies. They have used ultrasonic imaging to help them understand the mechanisms involved in swallowing disorders.

In another NIDR investigation, Dr. James M. Weiffenbach is investigating the ways in which people experience and perceive taste. Dr. Weiffenbach is currently studying how taste perception varies during the process of aging in humans. He and his colleagues are also evaluating the purported role of saliva in taste. Their work shows that saliva is not required for the maintenance of taste buds, but rather to dissolve foods and deliver tastants to the taste buds. Investigators are also evaluating oral sensory disturbances that occur in connection with disease, salivary gland dysfunction, or as an isolated complaint.

National Institute of Allergy and Infectious Diseases

Infectious diarrhea is a significant health problem in much of the world, particularly among infants. Diarrheal diseases such as dysentery, typhoid fever, cholera, and rotavirus infection are especially prevalent in developing countries. Research supported by the National Institute of Allergy and Infectious Diseases (NIAID) has contributed to our knowledge about infectious agents involved in diarrheal diseases and to the development of experimental vaccines against them.

Cholera is perhaps the most important cause of death from diarrheal disease because of the severe watery diarrhea produced by various strains of the bacterium Vibrio cholerae. Several cholera vaccines have been under development but they have not proven effective over long periods of time and they have been associated with adverse effects due to cholera toxins contained in the vaccine.

Using recombinant DNA techniques, scientists have produced vaccines that retained the ability to protect against cholera while excluding components known to produce toxins. These newly developed oral cholera vaccines have been tested in volunteers by Dr. Myron M. Levine, director of the Center for Vaccine Development supported by an NIAID contract at the University of Maryland in Baltimore. The vaccines are administered by mouth to achieve immunity in the gastrointestinal tract, where the bacteria take hold. Immunized volunteers were subsequently challenged with a strain of cholera. They were protected against infection, but a previously unrecognized toxin present in the vaccines was found to cause minor diarrhea. Field trials in Kenya using an oral vaccine are in the planning stages, but meanwhile Dr. Levine is continuing to test experimental vaccines that may prove to be free of the newly identified cholera toxin.

Diarrhea is a leading cause of illness and death among children under 5 years of age in many parts of the world. Infants hospitalized with acute diarrhea are generally treated with oral rehydration solutions to provide necessary fluid and to maintain electrolyte balance. Oral rehydration solutions recommended for use by the World Health Organization contain glucose, sodium, and a base of bicarbonate or citrate. Food is not usually given for 24 to 48 hours, in the belief that it might aggravate the diarrhea.

This regimen was recently challenged in an NIAID-supported study conducted by Dr. Mathuram Santosham of the Johns Hopkins University School of Medicine, and his colleagues at the Indian Health Service Hospital in Whiteriver, Arizona. Dr. Santosham gave babies with diarrhea a soy-based lactose-free formula after just 4 hours of oral rehydration therapy. He found that these babies had a greater than 50 percent reduction in stool output and a 40 percent shorter duration of illness compared to those receiving standard therapy.

In addition to improving the course of acute illness, nutrients provided by the formula would be especially important for undernourished infants or those in developing countries who may have diarrhea several times a year. Babies who are breastfed should continue to receive breast milk when they have diarrhea.

A less severe but common problem for adults is travelers' diarrhea, the most frequently encountered health problem among the estimated 8 million U.S. residents who travel each year to developing nations. Together with the NIH Office of Medical Applications of Research, the NIAID held a consensus conference in January 1985 on travelers' diarrhea. The consensus panel, chaired by Dr. Sherwood Gorbach of Tufts University in Boston, Massachusetts, considered whether travelers to developing countries should take antimicrobial drugs to prevent diarrhea.

Although diarrhea may sometimes be difficult for the traveler to avoid, the panel underscored the importance of avoiding potentially contaminated food and water--raw vegetables, raw meat, raw seafood, ice, unpasteurized milk--and recommended drinking bottled carbonated beverages and hot tea or coffee.

The panel also recommended that medications be obtained from a physician before traveling but used only when symptoms occur. In many cases, antidiarrheal compounds such as Lomotil or Pepto Bismol can provide fast relief. For more severe cases, antimicrobial drugs such as trimethoprim or doxycycline can be taken symptomatically to limit diarrheal illness to 1 or 2 days.

Travelers' diarrhea can be caused by many organisms, and one that is receiving increasing study is a parasite called Giardia lamblia. Giardia has also caused diarrheal disease in children who have attended day care centers and in people who have drunk contaminated water in the remote wilderness of Canada and the western United States.

NIAID scientists led by Dr. Theodore E. Nash are seeking to understand why some people infected with Giardia do not develop symptoms whereas others develop severe diarrhea and malabsorption. In addition, it would be important to know whether the same strains of Giardia can infect humans as well as other mammals, since it is thought that beavers are responsible for mountain lake and stream contamination.

Dr. Nash and his colleagues have used recombinant DNA technology to develop a test that enables them to recognize differences among various strains of Giardia. This technique will enable scientists to distinguish a nonepidemic strain from one that causes disease. Among the isolates studied to date, Dr. Nash has not found a species that appears to be unique to humans compared with other mammals.

National Institute of General Medical Sciences

The National Institute of General Medical Sciences (NIGMS) supports basic research and research training that provide the foundation for a better understanding of fundamental life processes. This research supplies new knowledge, theories, and concepts for the disease-targeted programs of other NIH Institutes.

NIGMS research programs encompass cellular and molecular biology, genetics, pharmacological sciences, and biophysics and physiological sciences. The Institute's Pharmacological Sciences Program supports research concerned with the cytochrome P-450 enzyme system of the liver--a system that is particularly important in drug metabolism since it helps transform foreign substances to less toxic compounds.

NIGMS grantee Dr. Curtis Omiecinski at the University of Washington, Seattle, is studying cytochrome P-450 genes. He is investigating how the genes for two cytochromes P-450 are expressed in rats and rabbits and how gene expression may change as the animal grows.

He has developed a highly sensitive method for detecting individual levels of the mRNA's (messenger RNA's--molecules that transmit genetic information from the cell nucleus to the cytoplasm, where protein synthesis takes place) for two cytochrome P-450 enzymes produced by the liver of an animal treated with phenobarbital. In the past it has not been possible to discriminate between these individual mRNA's or the genes for these two enzymes.

Using his new detection methods, Dr. Omiecinski has demonstrated that the livers of adult rats who have not been treated with phenobarbital contain very little or no detectable mRNA for either enzyme. In the livers of rats pretreated with phenobarbital, levels of these mRNA's rise dramatically. This indicates that the animals develop the biochemical means to metabolize doses of the drug after they are exposed to it.

In developmental studies, Dr. Omiecinski discovered that developing rat embryos do not have the ability to synthesize the enzymes in response to phenobarbital. They acquire this ability at birth and it remains through adulthood. These studies provide a means for examining the susceptibility of animals to toxic effects of chemicals and extend our knowledge of liver function.

Acetaminophen (the active ingredient in many nonaspirin-containing pain relievers such as Tylenol®) is generally regarded as safe in normal doses. However, if taken in excessive quantities, acetaminophen causes severe damage to the liver. NIGMS grantee Dr. Steven Cohen at the University of Connecticut, Storrs, is working learning more about the mechanisms by which acetaminophen causes liver cells to be destroyed.

By studying the livers of mice, as well as cultured mouse liver cells, Dr. Cohen has identified the endoplasmic reticulum (a cellular organelle that is involved in the storage, segregation, and transport of proteins manufactured by the cell) as the site of initial attack by the drug's metabolites (byproducts of metabolism).

These studies are among the first to identify subcellular sites of acetaminophen-induced biochemical alteration. Thus, they are a crucial first step in understanding acetaminophen toxicity in the liver and may eventually contribute to improving the drug and treating individuals who have taken overdoses.

National Institute of Child Health and Human Development

In its study of digestive conditions in infancy and early childhood, the National Institute of Child Health and Human Development (NICHD) places particular emphasis on the study of human breast milk. A coordinated research grant and contract program has been established to expand knowledge of the detailed composition and function of the many constituents of human milk and its importance in the development of normal and high-risk infants. As a result, this unique biological fluid is now recognized as a valuable source of nutrients, growth factors, and antimicrobial agents for newborn infants, particularly those of low birth weight. Other NICHD research priorities in the area of infant nutrition are discussed in the separate report on maternal and child health.

Discoveries continue to be made about the biochemistry of human milk. One milk enzyme, lipase, digests lipids (fats). NICHD grantee Dr. Margit Hamosh and her colleagues at Georgetown University in Washington, D.C., have discovered that lipases from a normal infant's mouth and intestines work together with milk-derived lipases to digest the lipids contained in milk and to attack the lipid surfaces of various intestinal parasites.

Studies of the mammary gland's role in the immune system have led to exciting information about the distribution, origin, and function of different cellular and soluble components of breast milk and how they affect the newborn's immune function.

In one study of almost 200 infants, NICHD grantee Dr. Pearay Ogra at Children's Hospital in Buffalo, New York, found that both breast-fed and bottle-fed infants who developed diarrhea showed similar recovery rates of the rotavirus from fecal specimens during a seasonal period of rotavirus infection. However, severe diarrhea was significantly more common among infants who were wholly or partly bottle fed. Bifidobacterial (normal bacteria in the intestine) growth, which appears to combat diarrhea, was much greater among breast-fed babies. The investigators suggest that breast milk may induce beneficial changes in the intestinal bacterial flora.

Researchers are investigating the mechanisms by which immunologic characteristics are transmitted from mother to infant via breast milk. Progress in this area has been made by NICHD grantee Dr. Leonard Seelig at the University of Texas in Dallas. Studies in rats have shown that immunologically active T-cells (lymphocytes) travel to the mammary gland during lactation and infiltrate the breast milk. When breast milk is ingested, some of the mother's lymphocytes contained in the milk travel through the infant's gastric membrane and become established in neonatal tissues. Further study will try to determine if these cells are also absorbed through the infant's

intestinal wall. An increased understanding of how the mother's lymphocytes, conveyed through milk, "seed" the infant's lymphoid tissue could provide a new means of controlling and preventing disease during the newborn period.

Other investigations focus on colostrum, the first milk produced by the nursing mother, to determine what effects colostrum's antibodies, antigens, and possible immune complexes have on the nursing newborn. Because the newborn's gastrointestinal tract is underdeveloped, immune substances may pass through it into the circulation, providing systemic immunity. Colostrum also affects maturation of the intestinal tract and the development of gastrointestinal defense mechanisms, which appear to be stronger in breast-fed babies. NICHD-supported researchers led by Dr. W. Allan Walker at Massachusetts General Hospital have determined that oral human immune substances can be safely given to infants and provide protection throughout the gastrointestinal tract. These findings will be valuable in the treatment of premature or very ill infants unable to breast feed.

Malabsorption syndromes and food intolerances are responsible for a great deal of infant sickness. To understand the causes of such problems, grantee Dr. Marian R. Neutra at Harvard University, is conducting studies to elucidate the function of cellular systems that are responsible for transporting large molecules through the lining of the small intestine. She has shown that these processes are associated with specialized cells in the different layers of the intestinal wall and are selective as to the types of molecules transported.

Infant colic is one of the most common problems encountered in pediatric practice today. Under a Small Business Innovative Research grant, Judith A. Bunge, affiliated with Sweet Dreems, Inc., in Westerville, Ohio, is developing a technique that uses motion to soothe colicky infants. In the first phase of the project, a clinical trial confirmed that a gentle vibrating device attached to an infant's bed reduced colicky episodes. The project, now in its second year, has the potential to produce a device that will be safe and effective in reducing colic.

Division of Research Resources

The recent discovery of a monkey model for both colon cancer and colitis is enabling scientists to explore possible causes of these poorly understood disorders and to develop new treatments.

This discovery was made by scientists at the Oak Ridge Associated Universities Marmoset Research Center in Tennessee who noticed an unusually high incidence of colon cancer and chronic colitis among cotton-top tamarins, small nonhuman primates native to South America. Shortly after this discovery was published, investigators at the New England Regional Primate Research Center (NERPRC) in Southboro, Massachusetts, confirmed the association of colon cancer and colitis in the cotton-top tamarin.

The NERPRC is one of the seven regional primate research centers (PRC's) supported by the Animal Resources Program (ARP) of the Division of Research Resources (DRR). The ARP helps meet the need of researchers for high quality, healthy animals and specialized animal research facilities.

The cotton-top tamarin is a convenient animal to study because of its naturally short generation span. Also, colitis and colon cancer produce similar tissue changes in the tamarin and the human. The animal model is unique, according to Laura V. Chalifoux of the NERPRC, because colon cancer develops following colitis in these animals as it often does in humans.

Several collaborative studies that explore potential causes of colitis and colon cancer are under way at both the NERPRC and the Oak Ridge facility. Scientists are examining the microflora present in the bowel of the cotton-top tamarin to determine if a microbe might cause colitis in this species. The expression of certain genes suspected of causing cancer is also being examined in this primate, as well as immunological changes associated with either colitis or colon cancer. Genetic records and breeding manipulations are being used to determine the role genetics might play in predisposing an animal to colon cancer.

Researchers collaborating with either the Oak Ridge center or the New England center are also testing various anti-inflammatory drugs on cotton-tops with colitis to determine if they can lessen the symptoms of the disease. This animal model allows drugs to be screened for effectiveness and side effects before these medications are administered to humans.

Because the cotton-top tamarin is an endangered species, its availability is limited, as are the kinds of studies that can be done on the animal; however, a variety of nonlife-threatening techniques, including x-rays, biopsies, and blood sampling, allow information to be gathered without endangering these animals.

Rather than reducing the number of these animals, biomedical research has had the opposite effect. The population of cotton-tops is dwindling dangerously in its native habitat of Colombia, but colonies of the monkey are breeding well at several primate centers and universities.

The study of colon cancer at the cellular level has also produced significant results. With funding from the National Cancer Institute and DRR's Biomedical Research Support (BRS) program, investigators led by Dr. Michael Brattain at Baylor College of Medicine in Houston, Texas, have discovered that colon cancer cultures secrete a compound that stimulates cell growth.

Crude extracts containing this compound stimulated the growth of normal mouse embryo cells in the laboratory. When the scientists purified these extracts, they were able to isolate both a transforming growth factor (TGF) and a tumor inhibitory factor (TIF). The TGF stimulated the growth of two of five human colon cancer cell lines. The TIF isolate, in contrast, inhibited the growth of the same cancer lines. TIF also inhibited the growth of an additional colon cancer line and one type of cultured skin cancer. Adequate quantities of TIF could completely stop the growth of all four cancer cell lines. TIF inhibited the growth of these tumor cells in a nontoxic way. It didn't kill the cells but, instead, induced them to differentiate to a greater degree.

Outlook

In addition to the research described in this report, NIH conducts and supports research on many other digestive diseases such as pancreatitis, esophagitis, malabsorption syndromes, liver cirrhosis, diverticulitis, and anorectal diseases. The known causes of digestive diseases range from infections, metabolic disorders, or genetic defects to neuromuscular disorders, toxins, and reactions to stress. As a result of the NIH's intramural research program and the awarding of extramural grants to scientists at universities and medical centers around the country, exciting new advances in digestive disease research continue to be made.